IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Estrada Garcia et al.

Serial No.: 10/501.697

Filed: July 16, 2004

For: METHOD OF STIMULATING GROWTH AND RESISTANCE TO DISEASES OF AQUATIC ORGANISMS

Examiner: Deborah K. Ware

Group Art Unit: 1651

Docket: 294-194 PCT/US/RCE II

Dated: January 21, 2010

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

DECLARATION UNDER 37 C.F.R. § 1.132

Sir:

I, INVENTOR, declare and say:

1. I am a co-inventor of the invention disclosed and claimed in the above-identified patent application, and an expert in the field of animal endocrinology.

2. I am Head of the Animal Biotechnology Division, at the Center for Genetic Engineering and Biotechnology, Havana, Cuba.

3. As an expert, I have been contacted by officials from Assignee asking my opinion whether a person of average skill in the art of animal endocrinology would understand at the priority date of the above-identified patent application, i.e. January 24, 2002, that GHRP-6 when administered to fish would have the same repertoire of effects as described for 2-acylaminopropanamide secretagogues.

4. In addition, I have been asked by officials from Assignee to provide my opinion on the issue whether a person of average skill in the art of animal endocrinology would understand at the priority date of the above-identified patent application, i.e. January 24, 2002, that GHRP-6 when administered to fish would have the same repertoire of effects as the actual growth hormone for which it is a secretagogue.

5. Further, I have been asked by officials from Assignee to provide my opinion on the issue whether a person of average skill in the art of animal endocrinology who is familiar with the known and potential uses of growth hormone such as stimulation of the immune system in companion animals and who is aware of the fact that the administration of 2-acylaminopropanamide secretagogues for the purpose of stimulating the release of endogenous growth hormone can have the same effects or uses as growth hormone itself, would understand at the priority date of the above-identified patent application, i.e. January 24, 2002, that the administration of a GHRP-6 to fish and crustaceans would result in stimulating resistance to diseases in these animals.

6. I have read and understood

- the specification and claims of US Serial No. 10/501,697;

- the Office communications as issued by the USPTO on 07/22/2009;

- the disclosure of Hipskind et al (US 5773441), and

- the set of claims as filed on 05/08/2009.

7. The question pertains to the issue whether it would be obvious the person skilled in the art of animal endocrinology and who is aware of the teaching of Hipskind et al. to use GHRP-6 for stimulating the resistance to diseases in fish and crustaceans; or to use GHRP-6 for decreasing the intensity and extension of pathogen invasion in fish and crustaceans.

8. First, it should be noted that there is a distinction between the "prophylactic use" of GHRP-6 according to the present invention through "stimulation of resistance to

diseases" in fish and crustaceans, and the "therapeutic use" of a totally different group of secretagogues (the 2-acylaminopropanamides) as disclosed in Hipskind.

9. I note that Hipskind indicates that immune-suppressed human subjects are treatable with growth hormone. That is not surprising because it is known that the peptidyl secretagogue GHRP-6 stimulates growth hormone release in humans (vide also column 2, lines 28-40 of Hipskind). Immune-suppression relates to a deficiency in the immune system, and treating immune suppression relates to neutralizing that deficiency, which is quite something different from stimulating resistance to diseases. The teaching of Hipskind is directed to non-peptidyl 2-acylaminopropanamide secretagogues (vide column 42, line 64 of Hipskind). Hipskind merely refers to the fact that GHRP-6 is a growth hormone releasing peptide that may be used in combination with the non-peptidyl 2-acylaminopropanamide secretagogues. Hipskind does not provide any new incites into the effects of GHRP-6, and does not indicate anything about the effect of GHRP-6 in other species than humans.

10. With respect to growth hormones in general, Hipskind states that the "compounds employed in the present invention for the purpose of stimulating the release of endogenous growth hormone can have the same effects or uses as growth hormone itself. These varied uses of growth hormone may be summarized as follows:" (following is an elaboration of the various known effects of growth hormones). The term "compounds" should be understood in the context of column 2, line 47 of Hipskind, where the term is used to refer to the non-peptidyl secretagogues (the 2-acylaminopropanamide secretagogues), and thus not to GHRP-6. Also, the elaboration has no bearing to any effects of GHRP-6 per sé, and certainly not in relation to fish and crustaceans.

11. Hipskind also states that 2-acylaminopropanamide secretagogues can have the same effects or uses as growth hormones, such as treating immuno-suppressed patients (column 43, lines 44-45). The skilled person, who reads the disclosure of Hipskind will certainly not conclude from column 43, lines 44-45 that GHRP-6 will stimulate resistance to diseases in fish and crustaceans. It cannot possibly be that the link thereto is provided by the mere reference to the phrasing that the "compounds employed in the present invention are preferred for human pharmaceutical uses as well as veterinary uses, particularly in cattle,

swine, sheep, poultry and fish." After all, at the time of Hipskind there was no evidence at all in the art that use of GHRP-6 in fish would be useful.

12. I note that Hipskind et al do not teach that i) fish are treatable with GHRP-6; ii) that GHRP-6 is an effective agent in animal husbandry; iii) that GHRP-6 is orally active; or iv) that GHRP-6 stimulates resistance to disease. Hence, Hipskind does not and cannot teach or suggest that GHRP-6 will stimulate resistance to diseases in fish and crustaceans. After all, it was not known at the time the Hipskind application was filed (1996) that a receptor for GHRP-6 was present in fish.

13. In order to substantiate that the present of a receptor for GHRP-6 in fish (now known as the ghrelin receptor) was unknown at the time of Hipskind, I enclose a review paper of Kaiya et al. 2008 (copy enclosed), entitled: "Ghrelin: A multifunctional hormone in non-mammalian vertebrates". I particularly point at the left column of page 118 of that article where it is stated that:

> *"Among non-mammalian vertebrates, GHS-R has been reported in two species of teleosts, black seabream and a pufferfish, and in a bird, chicken (Figs. 3 and 4). In the black seabream, both types of receptor, GHS-R1a (385 amino acids (aa)) and GHS-R1b (295 aa), have been identified (Chan and Cheng, 2004; Chan et al., 2004b). In a pufferfish, Spheroides nephelus, GHS-R1a ortholog, namely 78B7 (374 aa) has been reported (Palyha et al., 2000)".*

14. Thus, at the time the Hipskind application was filed (1996) the ghrelin receptor in fish was not known. The first sequence for the ghrelin receptor (*GHS-R)* in fish was disclosed in year 2000, in the reference of Palyha et al., 2000 (copy enclosed). Palyha et al stat on page 166, right column:

> *"Finally, in all species tested, from chickens to humans, and now in Pufferfish, the GHS-R pathway has been functionally conserved. In spite of the lack of direct proof, the collective evidence that supports conservation of a physiologically important natural ligand for the GHS-R is overwhelming."*

Thus, Palyha et al. were the first (in 2000) to establish that fish had a homologue of the GHS-

Receptor.

15. Hence, Hipskind and his coworker could not possibly know at the priority date whether GHRP-6 was able to interact with the receptor in fish or not. This means that the suggested use by Hipskind of the 2-acylaminopropanamide secretagogues in fish (see column 3, lines 60 - 65), for which the Hipskind disclosure provides not a single basis, will certainly not give the idea to the skilled person to use GHRP-6 in fish, let alone that the skilled person would be motivated to use GHRP-6 for stimulating the resistance to diseases in fish and crustaceans; or to use GHRP-6 for decreasing the intensity and extension of pathogen invasion in fish and crustaceans.

16. A potential therapy based on 2-acylaminopropanamides as disclosed in Hipskind can provide no prediction for an efficacy of a similar therapy based on a GHRP-6. Now that Hipskind also does not disclose the stimulation of resistance to diseases" in fish and crustaceans by GHRP-6, I am of the opinion that the claims are not obvious in view of Hipskind et al.

17. I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true. Further that these statements were made with the knowledge that willfully false statements, and the like, made are punishable by fine or imprisonment or both under Section 1001of Title 18 of the United States Code, and that such willfully false statements may jeopardize the validity of the application of any patent issued thereon.

Date: January 19, 2010

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